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DISCUSSION ON THE NEURONE DOCTRINE IN ITS RELATIONSHIP TO DISEASE OF THE NERVOUS SYSTEM.

(*a*) THE ANATOMIC-CYTOLOGICAL RELATIONSHIP OF THE NEURONE TO DISEASE OF THE NERVOUS SYSTEM.*

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In view of the papers which are to follow, the present one may perhaps be most serviceable if it be limited to a statement of some of the principal facts of the general anatomy of the nervous system as at present understood, and a few remarks with regard to the nature and significance of the neurone doctrine in connection with these.

It may be considered as established to-day that the nervous system, like all other parts of the body, consists of cells and of intercellular substances. Aside from the covering membranes of the brain and spinal cord, the blood and lymph vessels of the nervous system, and the slight amount of connective tissue which accompanies them, as well as the cellular sheaths of the axis-cylinder processes and cell-bodies of the peripheral cerebro-spinal nerves and of the sympathetic system, all of the morphological elements in the nervous system are to be regarded as derivatives of the ectoderm of the embryo. Among these ectodermal derivatives can be distinguished two principal varieties of cells:

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(1) That which includes the supporting elements of the nervous system, namely, the neuroglia and the ependyma, and (2) that which includes the true nerve-cells or neurones.

The supporting cells and the true nerve cells are very simple in form in the beginning of development; later on, they undergo remarkable changes in form, distribution and arrangement. The ependyma cells are transformed to the long-drawn out structures so familiar in Golgi preparations. The neuroglia cells assume variable shapes, and give rise to specific cell-products—the so-called neuroglia fibrils—parts of which may even become extra-cellular. The true nerve-cells or neurones wander for shorter or longer distances from their breeding-places; they are sometimes aggregated in groups or layers, sometimes very irregularly distributed; they exhibit extraordinary variations in form, the protoplasm becoming manifoldly divided so as to give rise to (1) a relatively abundant mass—the so-called perikaryon—containing the nucleus, centrosome and archiplasm, (2) a group of relatively short processes—the so-called dendrites—resembling the perikaryon closely in minute structure, and (3) one or more processes which do not divide until at some distance from the cell-body—so-called axones—which differ somewhat in external form and internal structure from the dendrites, in that they are in general more delicate, are devoid of the so-called tigroid substance, and often extend for great distances from the perikaryon, in which event, except in the sympathetic nervous system, they become surrounded for the larger part of their course with a fatty or myelin sheath.

Inside a single tissue there is perhaps nowhere in the body as much variability in the elements in different parts as in nerve tissue. Muscle-cells are strikingly alike in all the voluntary muscles of the body, liver-cells in the right lobe are indistinguishable from those in the left lobe. Even in the kidney, where there are distinct variations in the cells lining different parts of the tubules, the general habitus is very similar.

The nerve cells of various parts have, however, a specific stamp; they can be recognized at a glance; they subserve specific functions. Like other cells in the body, except those of the blood and perhaps a few others, each nerve-cell or neurone, though possessing an individuality of its own, stands in intimate anatomical and physiological relations to other cells. The cells of epithelial tissues, for example, are related to one another by direct contact or by means of intercellular protoplasmic bridges, or by both methods. Many cartilage cells are connected with one another by fine protoplasmic threads. The nerve-cells or neurones are occasionally connected with one another by coarse strands of protoplasm (especially in the retina), much more often by means of intimate protoplasmic relations existing between the terminals and collaterals of the axone of one nerve cell or neurone, and the dendrites and perikaryons of other nerve-cells or neurones. Several forms of the latter relation have been studied: (1) the large calyx-like expansion of an axone terminal upon a cell-body (perikaryon) with apparent fusion or concrescence of the protoplasm of the two; (2) the intimate apposition and possible fusion of fine terminals of axones and collaterals with dendrites and perikaryons, sometimes apparently by means of a fine-meshed anastomosing network formed by the former, and (3) the passage of extremely minute, though uninterrupted, fibrils from one nerve-cell or neurone into another, or even through a series of nerve-cells or neurones, possibly through all the cell-units of the whole nervous system. Whatever may be the conclusion ultimately arrived at with regard to the interneuronal relations of the whole nervous sytem, one thing is certain, the relations between certain groups of neurones is very direct, so that we can distinguish firmly established conduction paths composed of superimposed and subimposed sets of nerve-cells or neurones. This is an organic memberment easily determinable by the methods at present at our disposal; its recognition has led to important advances in our knowledge of neutral anatomy, physiology and pathology. The various afferent conduction paths, the motor conduction path from the cortex of the cerebrum to the voluntary muscles, the conduction paths upon the integrity of which many of the reflexes depend, as well as some of the more complex associative conduction paths are now tolerably well understood; the chains of nerve-cell units or neurones, of which they are composed, have been localized; the integral links (or individual neurone systems) of each chain are being carefully studied.

A study of the historical development of a subject alone can give the clue for proper valuation of single contributions made to it. The influence of the introduction of the neurone-conception upon the shaping of neurological ideas as they exist at present can only be appreciated when the origin, course, and present status of that concept are considered. The history of the inception does not date back for a very long period, but it originated earlier than is generally supposed, having as it did a strong foundation in the minds of pathologists and embryologists many years before Ramón y Cajal began to publish the results of his work with the chrome-silver method of Golgi, and longer still before Waldeyer brought all the evidence in favor of the conception together, and gave to it a distinctive name.

The anatomical darkness in which investigators groped from the time of Soemmering (1798), to that of Deiters (1865), has recently been fully discussed by Stieda.[1]

It is a pathetic process to wade through the vague descriptions of those days; the glimmerings of form relations here and there met with seem to us but very illiberal reward for the patience, industry and conscientiousness which characterized the work of those earlier investigators. Research centered about the "nerve-cells," the "nerve-fibers," and the relations of the latter to the former. The more notable contributions came from Ehrenberg, Purkinje, Valentin, Remak, Schwann, Hannover, Stilling, Helmholtz, von Kölliker, Wagner, Bidder, Gerlach, Schroder van der Kolk and Lockhart Clarke. With Deiters came light. The advent of his "Theorie der centralen Ganglienzelle" marks an epoch in neurology. He distinguished sharply between the protoplasmic processes and the axis-cylinder process of the central ganglion cells. Though foreshadowed by the views of Remak, Wagner and Helmholtz, the precise, objective descriptions of Deiters may fairly be regarded as by far the most influential in leading up to the modern conception of the nature of the biological unit in the nervous system.

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[1] Stieda, L.: "Geschichte der Entwickelung der Lehre von den Nervenzellen und Nervenfasern während des XIX Jahrhunderts. I Teil von Soemmering bis Deiters." Festschrift zum siebenzigsten Geburtstag von Carl von Kupffer. Jena, 1899.

The cell theory was founded in 1838 by Schleiden, and supported and extended in 1839 by Schwann. It underwent later important corrections in the hands of Max Schultze, who developed the protoplasm theory. Virchow's twenty lectures on cellular pathology perhaps did most to inculcate the doctrine of "vital units" in the minds of medical men, making, as he did, the cell the starting point for the investigation of physiological and pathological problems. The world avowedly accepted the cell doctrine for the whole human and animal body; tacitly it did not accept it for the nervous system, for there were always the troublesome fibers. "Nerve-cells" were talked about; they were unipolar, bipolar and multipolar; "nerve fibers" were talked about, and some of them were known to be processes of nerve cells. No precise conception of the extent of a "nerve cell" or of the relation in general of "nerve fibers" to "nerve cells" had yet been arrived at. Ideas were vague; anatomical conceptions were confused.

Neuro-pathology came to the rescue. Out of the observations of Waller and Türck on secondary degenerations came the idea of trophic domains with the nucleated "nerve-cell" as a center. Disease processes affecting the nervous system electively confine themselves to certain definite territories. Von Gudden's experiments on young animals supplemented the studies of secondary degeneration by those of secondary atrophy. The doctrine of system diseases developed. Gowers introduced his conception of the "upper motor segment" and the "lower motor segment." Certain "cells" in the cerebral cortex and the "fibers" of the pyramidal tract correspond to the "upper segment"; the "multipolar ganglion cells" of the motor nuclei of the brain and cord, together with the motor "nerve fibers" of the peripheral cerebrospinal nerves constitute the "lower segment."

Anatomical and embryological studies were progressing. Flechsig was finding that his study of the serial sequence of the medullation of bundles of nerve-fibers in the central nervous system was isolating tracts of nerve fibers, which corresponded in a striking manner with the degenerative processes met with in elective nervous diseases. His made his epoch-making discovery that the nerve-cells in development are at first devoid of processes; that they wander as independent cell-units from their birthplaces; that after a certain time cell-processes are developed—an axis cylinder process first and protoplasmic processes or dendrites later; that the axis-cylinder processes of all nerve fibers are to be regarded as outgrowths from, and, therefore, as constituent parts of, nerve cells; and, finally, that all connections of a nerve fiber, other than that with the cell-body, which gives it origin, are either indirect or have arisen secondarily. The first fruits of the wonderful Golgi method were being gathered. The sharp black silhouettes of the nerve-cell body and of the complex processes connected with it were beginning to excite attention outside of Italy.

Just at this juncture appeared the brilliant and far-seeing article of Forel.[2]

In "Einige hirnanatomische Betrachtungen und Ergebnisse" he developed in a most forcible manner the doctrine of *the individuality of the nerve elements;* the *unit* in the nervous system includes not only the "nerve-cell" of the books, but also the processes which depend for their nutrition upon it, including the axis-cylinder process of a nerve fiber, as far as the degeneration can be traced. The limits of a given degeneration in a pathological process correspond in extent to those of the nerve-unit or units involved in the lesion. The papers of Forel and His mark the beginning of the downfall of the old views which separated so sharply the "nerve cells" from the "nerve fibers." The "nerve cell" and the axis cylinder of a "nerve fiber" were seen to represent parts of a single anatomical and physiological unit.

In the years which immediately followed Santiago Ramón y Cajal began to pour forth that steady stream of contributions to the anatomy of the nervous system which has excited the admiration and compelled the gratitude of every one interested in the solving of neurological problems. Golgi had devised the method and had led the way to great results. He had described the two main categories of nerve cells (Type I and Type II), discovered the side-fibrils, and made exhaustive studies of the neuroglia. Ramón y Cajal used chiefly the rapid Golgi method. The great value of his work lies in the systematic objective study of a great many different parts of the nervous system by the chrome silver method. Paper followed paper in which, one after another, the spinal cord, the retina, the cerebral cortex, the cerebellum, the corpora quadrigemina, the olfactory lobes, the medulla oblongata and pons, and the sympathetic system were examined and the results yielded by the especial method faithfully recorded. In after years, when the neurological history of these times shall be written, it would seem likely that Ramón y Cajal's name will be most remembered on account of his notable contributions to the special microscopic anatomy of various parts of the nervous system rather than to its general histology. At the time of their appearance, however, these articles attracted more attention from the side of general histology than from that of microscopic anatomy. Ramón y Cajal denied the existence of a diffuse nerve-network in the sense of Golgi, as Golgi before him had denied the existence of a diffuse nerve-network in the sense of Gerlach. He challenged Golgi's ideas of the morphological distinctions between sensory and motor cells. He asserted that in Golgi preparations, except perhaps in the sympathetic system, and in some insects, neither dendrites nor axones could be seen to anastomose with one another—all ended by free terminations in, among, or upon the cell-bodies or branches of other nerve-units. He believed, therefore, from the chrome silver pictures that the nerve-units, aside from the exceptions mentioned, are completely independent of one another. His description of the forms and mode of branching of the units in the most diverse parts are by far the most complete which have been contributed by a single investigator. A large part of his succcess depended upon his application of the silver method to embryonic tissues and to the tissues of a series of animals. His views were in large part accepted by von Kölliker, von Lenhossék, van Gehuchten, Retzius, Schäfer and

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[2] Forel, A., "Einige hirnanatomische Betrachtungen und Ergebnisse." Arch. f. Psychiat., Berl., Bd. XVIII (1887), S. 162-198.

Berkley, all of whom made important contributions along similar lines.

The studies in the comparative anatomy of the nervous system undertaken by Bela Haller, Nansen, Fusari and Retzius lent support to the views above mentioned. The methylene blue method of vital staining introduced by Ehrlich was also confirmatory, at least in many respects.

In 1891 Waldeyer[3] published a collective review of the observations made up to that date and stated as the main results (1) that the axis cylinders of all nerve fibers (motor, secretory and sensory), conducting centrifugally or centripettally, have been proven to proceed *directly* from cells; a connection with a fiber network, or an origin from such a network, does not exist; and (2) that all these nerve fibers end free, with "end-arborization" (Kölliker), without the formation of networks or anastomoses. Combining the two, he suggests that "the nervous system consists of numerous nerve-units (neurones) not connected with one another anatomically or genetically. Each nerve-unit consists of three parts—the nerve cell, the nerve fiber and the end-arborization. The physiological conduction-process can run either in a direction from the cell to the end-arborization or in a reverse direction. The motor conductions run only in the direction from the cell to the end-arborization, the sensory sometimes in the one, sometimes in the other direction." He acknowledges that his ideas of the mode of conduction are based on the view that no anastomosing nerve networks occur, but only a nerve feltwork (neuropilema, His). He states, however, that "if we assume with Golgi and B. Haller the existence of nerve networks, the view is modified somewhat, but we can still retain the nerve-units. The limits between the two nerve-units would then always lie in a nerve net-work and, anatomically at least, be not exactly definable by our present methods."

It is obvious that the essential feature of the whole work up to this time, and this is the point that Waldeyer wishes to emphasize, is the demonstration of the existence in the nervous system of definite *nerve-units.* The view arrived at by the pathologists and embryologists here found its histological support. The nerve-unit (Waldeyer's neurone) consists of three parts, the "nerve-cell," the "nerve fiber" and the "end-arborization." In my opinion,[4] already expressed in several places, this doctrine of the nerve-units (Waldeyer's neurones) is *nothing more or less than the application in full of the cell-doctrine to the nervous system.* The "nerve-cell" of the books is only a part of the *real* nerve-cell. The "nerve-units" of Forel and of Waldeyer are the *complete* nerve-cells. The introduction of the term nerve-unit or neurone was a happy hit; the name spread like wild-fire and with it the important conception of the nature and extent of the unit. Scarcely in any other way could the old confusion as to the cell-unit arising from the use made of the terms "nerve-cell" and "nerve-fiber" have been so quickly done away with. The failure to recognize the cell-body and the axis cylinder process of a nerve fiber as integral parts of a single cell would have been but slowly corrected had we not had a new name. Even now if we teach beginners that these complete units are nerve-cells they are too often puzzled by the text books, nearly all of which write of nerve-cells and nerve-fibers according to the old usage. The suggestion of Schäfer and Sherrington to use the word "perikaryon" to replace the word "nerve-cell," as formerly used, is a good one. Either this word or the term "cell-body" should certainly be employed and the term "nerve-cell" reserved to indicate the whole nerve-unit or neurone. Should this be happily accomplished the terms "nerve-unit" and "neurone" could, if desired, be dropped, for they would then have served their purpose.

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[3] Waldeyer, W., "Ueber einige neuere Forschungen im Gebiete der Anatomie des Centralnervensystems." Deutsche med. Wchnschr., Leipz., Bd. XVII (1891), S. 1244, 1267, 1287, 1331, 1352.

Following upon the establishment of the doctrine of nerve-units or neurones came several accessory theories which have been widely diffused and which by a number of workers have come to be regarded as actually a part of the nerve-unit or neurone doctrine. Among these may be mentioned (1) the theory of the complete independence of the nerve-units from one another except by contact or contiguity; (2) the theory of the ameboid movement of the processes of the nerve-unit or neurone—often known as the "retraction theory," and (3) various theories concerning the structures in the nerve-unit or neurone which take part in the conduction processes in the nervous system.

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[4] Barker "On the Validity of the Neurone Doctrine." Amer. J. Insan., Balt., 1898-9, vol. LV, pp. 31-49. "The Nervous System and its Constituent Neurones." N. Y., D. Appleton & Co., 1899—"Progress of Neurology," Phil., M. J., Jan. 28, 1899.

As a matter of fact, most of the objections which have been advanced against the neurone doctrine have in reality been urged against one of these accessory theories rather than against the conception of the nerve-unit or neurone *per se*.

ad. 1.—The theory of relation by contact only among morphologically completely independent units was built up almost entirely upon microscopic pictures obtained by Golgi's method. As we know now, this procedure, while yielding magnificent results with regard to the principal points concerning the external morphology of the neurone, is insufficient to give information concerning the more minute relations which exist at the points where the terminals of the processes of one nerve-unit come into relation with other nerve-units. It has been established by other methods:—

(a) That coarser anastomoses occasionally occur between the dendrites of different neurones;

(b) That the terminals of the axone and collaterals of one neurone enter into very intimate protoplasmic relations with the perikaryons and dendrites of other neurones (Held's concrescence);

(c) That fibrillary structures can be seen, when the tissue is stained by certain methods, passing from one nerve-unit or neurone into another.

The "contact theory" is still vigorously supported by a number of neurologists, notably by Semi Meyer.[5] The evidence brought forward by Dogiel, Held, Apáthy and Bethe is, however, so strong that the contact-theory or theory of complete morphological independence of the nerve-units or neurones must be considered as having a very doubtful basis, if not as actually refuted. Considering what we know of the intercellular bridges and protoplasmic fibrils which connect other cells with one another in other parts of the body, it would be surprising if the nerve-cells or neurones were not similarly connected. As will be recalled from the quotation from Waldeyer cited above, that anatomist did not make the doctrine of the nerve-units or neurones contingent upon absolute histological independence, but stated that "even if networks or anastomoses exist we can still retain the nerve-units." In this connection the lucid statement of Carl Weigert,[6] whose sound judgment many will be willing to trust, may be recalled. He says: "The interesting doctrine of the independence of the 'neurone' has nothing to do with the doctrine of free terminations. This is simple enough, since the doctrine of the neurones, although not under this excellent name, long before Golgi's method was thought of, was well known in pathological anatomy. The whole doctrine of the typical secondary degenerations rested entirely upon what we now call the neurone doctrine. We knew long ago that on destruction of the central gyri or any other part of the pyramidal tract, only those parts of the pyramidal tract degenerated which were cut off from their cell-bodies of origin. We knew long ago that the motor nerves stand under the trophic, or, as it is now called, idioplastic, influence of the cells of the ventral horns only, the sensory under that of the spinal ganglion cells, and that all these nerve-tracts, and no others, degenerate after separation from their idioplastic center.

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[5] Meyer, S., "Ueber centrale Neuritenendigungen." Arch f. mikr. Anat., Bonn, Bd. LIV (1899), S. 296.

"The system of any idioplastic (trophic) center, with its territory, is, however, exactly identical with one neurone. Whether the processes of two neurones adjoin one another directly, or are separated from one another by a small interspace, may have a slight anatomical interest; biologically it has none."

ad 2.—The so-called "retraction-theory" may be dismissed with a word. It never had a basis in observation or experiment, for the note of Wiedersheim can scarcely be regarded as such. With the demonstrations of the intimate relations between neurones brought by the preparations of Held, Apáthy and Bethe all plausibility to the theory disappears. The only wonder is that a theory with so little objective support should have been so widely diffused and so extensively employed for the explanation of physiological and pathological conditions.

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[6] Weigert, C.: "Die histologische Technik des Centralnervensystems." Merkel-Bonnet's "Ergebn. d. Anat. u. Entwickelungsgesch.," Wiesbaden, Bd. V (1895), p. 28.

ad 3.—Coincident with the variation of views concerning the minute internal structure of the nerve-cell protoplasm, a number of theories as to the physical basis for conduction have originated. Max Schultze[7] had asserted that the axis cylinder and the ganglion cell possessed a fibrillary structure, and there early developed a view that these fibrils represent the conducting substance. Nissl believed that the "unstainable substance" in his methylene blue preparations must be regarded as the functionally essential part of the cell. Held thought that the whole protoplasm might conduct, but did not deny that the longitudinal beams of the protoplasmic meshwork might offer channels of lower resistance to conduction than others.

An enormous stride forward has, however, been made by Stefan Apáthy[8] of Kolozsvár through the introduction of new technical methods and thorough application of them to the nervous tissues of certain animal types. The distinguished Hungarian investigator began these studies as early as 1884, and since then has made a number of publications, the most complete article being that published from Naples in 1897.

A succinct epitome of his researches and their general bearings was given by Apáthy[9] in his address before the International Congress of Zoology in Cambridge in 1898. His demonstration of the neurofibrils and their relations to the nerve-units represents the most important discovery in neurological anatomy in recent years. I[10] have so recently reviewed the principal features of Apáthy's work that it will be unnecessary to go at this time into its details. Apáthy's methods demonstrate histologically the "neurofibrils" and their constituent "elementary fibrils" most exquisitely; to see his specimens is to be convinced of the existence of these structures as most definite morphological entities. The elementary fibrils form networks in the perikaryons of nerve-cells; there is no beginning or end to the fibril system, it is a continuum. Fibrils may even exist outside the nerve-cells forming a meshwork—his so-called *Elementargitter*—in invertebrates.

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[7] Schultze, M.: Article in S. Stricker's "Manual of Histology," American transl., 8vo, New York, 1872.

[8] Apáthy, S.: "Studien ueber die Histologie der Najaden." Math.-naturw. Abth. d. ung. Acad. d. Wissensch., 1884, "Das leitende Element des Nervensystems und seine topographischen Beziehungen zu den Zellen. Mittheil. aus der Zool. Station zu Neapel." Bd. XII (1897), H. 4, S. 495-748.

[9] Apáthy, S.: "Ueber Neurofibrillen." "Proc. Internat. Congr. Zool.," Cambridge, 1898, pp. 125-141.

In addition to his demonstration for the first time of the neurofibrils in invertebrates, Apáthy has brought all the proof that can be adduced from the morphological side alone that the neurofibrils represent the conducting element in the nervous system. In his Cambridge address he summarizes the evidence in favor of the conducting nature of the neurofibrils as follows:

(1) The specificity of the neurofibrils.

(2) The continuity of the neurofibrils.

(3) The behavior of the neurofibrils in the ganglion cell.

(4) The entrance, and, as a matter of fact, the exclusive entrance, of the neurofibrils into the sense cells and their specific topographical relations in the body of the sense cell.

(5) A penetration of neurofibrils into the depth of the muscle fibers and their specific topographical relations to the sarcoplasm.

(6) The behavior of the neurofibrils in the gland cells.

(7) In the cells which form the wall of vessels devoid of muscle.

(8) The relations of the neurofibrils to various other epithelial cells.

(9) The extra-cellular continuation of the neurofibrils, the branchings and reciprocal relations of the same to the center.

(10) The same to the periphery.

(11) The nerve paths consist in places exclusively of neurofibrils.

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[10] In "The Nervous System and Its Constituent Neurones," N. Y., 1899.

(12) The intimate relation between the length of the distance traversed by a neurofibril in a certain specific cell variety and the developmental stage of the organ, the chief constituents of which are those specific cells.

Apáthy's work abounds with objective descriptions of the topographical relations of the neurofibrils to the cells and outside the cells in the organism. The above researches alone would suffice to indicate the great advance made by this investigator, but in addition his various articles contain a mass of details concerning the finer anatomy and histology of the nervous system and of the sense organs of several types of animals, especially of the leeches. His studies of the neurofibrils in Lumbricus and in the Hirudineæ are among the most important parts of his work.

It is pleasing to be able to report that Apáthy's views do not in any way conflict with the cell doctrine. His objection to the neurone doctrine is evidently based upon the opinion that it includes also the theory of contact relation or the doctrine of completely isolated units. In a personal communication recently received he states his position as follows: "The neurofibrils are a specific cell product and are distributed originally everywhere only with the processes of these cells; besides, these processes later consist for long distances and at their extremities only of neurofibrils and interfibrillar (or perifibrillar) substance. My opposition to the neurone theory consists solely in this, that I can demonstrate that these processes with their neurofibrils also pass through other cells or that the neurofibril reticula (*Neurofibrillengitter*) of different cells are connected with one another by means of neurofibrils; that therefore the neurones are not isolated units either in an anatomical or in a functional respect. What there is left over of the neurone doctrine is common to it and the cell doctrine in general; and that is the trophic and other regulatory influence of each definite domain, the center of which is the body of a ganglion cell and within which occur the constituents of the nervous system belonging genetically to the ganglion cell. This I have never denied, but it is simply the cell doctrine; there is nothing specific for the neurones."

Other investigations on neurofibrils have been made by

Becker, Dogiel, Mann, Kronthal and Bethe. The results of the last-named histologist[11] are among the most interesting. Acquainted with the researches and methods of Apáthy, Bethe has undertaken the study of the vertebrate and human nervous system with highly satisfactory consequences. By a specially modified method he is able to differentiate the neurofibrils in human tissues in a manner surpassing by far anything hitherto attained. In the main his findings agree with those of Apáthy, the chief differences being that Bethe does not find the inner network of fibrils in the cell-body, and that he thinks the *Elementargitter* is not "diffuse." If the neurofibrils are the true conducting element in the nervous system, the findings of Bethe with regard to their distribution in the dendrites is interesting as refuting the theory of exclusively cellulipetal conduction in these processes. In Bethe's specimens not all the fibrils entering the cell body by way of the dendrites pass out by way of the axone; many pass out by way of another dendrite. Fibrils can even be followed along one branch of a dendrite into another branch of the same process without entering the perikaryon at all.

Strongly in favor of the view that the neurofibrils are the conducting elements is the observation of Bethe and Möncke-berg[12] in which they make out that at the nodes of Ranvier all constituents of the nerve-fiber are interrupted except the neurofibrils. The perifibrillar substance is absent here, they asssert, just as is the myelin sheath and the neurilemma.

Bethe's standpoint with regard to the neurone doctrine is easily understood. He denies the existence of histologically completely independent units, but retains the name for all the parts easily demonstrable as standing in connection with one ganglion-cell body.

Of the more important of the recent reviews of the neurone doctrine may be mentioned those of Adolf Meyer;[13] von Lenhossék;[14] Hoche;[15] Nissl,[16] and Edinger and Wallenberg.[17] The conceptions of the neurone doctrine entertained in these different articles vary somewhat, but all but Nissl retain the conception of the nerve-units. Nissl, in the article in which he developes his theories concerning the gray matter, violently throws the neurone doctrine overboard, maintaining that it is utterly refuted. He appears to see in it only the contact-theory and to have misconceived or lost sight entirely of the real significance of the doctrine of nerve-units. Edinger, on the other hand, as might have been expected, grasps the situation very clearly. To quote from him:

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[11] Bethe, A.: "Die anatomischen Elemente des Nervensystems und ihre physiologische Bedeutung." Biol. Centralb., 1898, S. 843.

[12] Bethe, A.: u. Mönckeberg. "Die Degeneration der markhaltigen Nervenfasern der Wirbelthiere unter hauptsächlicher Berücksichtigung des Verhaltens der Primitivfibrillen (Zugleich ein Beitrag zur Kenntniss der normalen Nervenfasern)." Arch. f. mikr. Anat., Bonn, Bd. LIV, S. 135.

"The neurone theory was deducible in the first place from the results of degeneration pictures (Forel). Indeed, it was long silently accepted by the pathologists before we had the word neurone, the pathologists having recognized that injury of any given nerve or of any cell is never followed by more severe and more direct consequences, beyond a certain domain. It has been customary to look upon this domain as dependent upon the cell nucleus of a definite ganglion cell and then to view the whole unit as trophic. When the proof was brought, chiefly by S. Ramón y Cajal's investigations, that such units could also be distinguished anatomically, the anatomists were justified also in becoming very much interested in the conception that the whole nervous system might be built up of a series of superimposed cell units. From many sides findings which spoke in favor of this were reported, justifying the conception to which Waldeyer, after reviewing all the facts, gave the name of the neurone theory. Whether the ends of the neurone are free, as the majority supposed, or whether here and there or even always genuine fusions with neighboring nerve units occur, have been much discussed questions. The majority have, as is well known, declared in favor of a free splitting up of the cell processes around the body or the processes of other cells. But at the time of this report we have learned through Held, Golgi and others that at the periphery of the cell much more complicated relations can be found than correspond to so simple a view. It appears to us as of secondary importance whether one can or not to-day demonstrate everywhere the anatomical limits of the nerve domain dependent on the single ganglion cell, as long as no fact is brought forward which interferes with the conception of the neurone as a biological unit. Such a fact does not exist, however. Indeed, all the pathological relations known at present when the ganglion cell and its processes degenerate can only be explained when one stands on the platform of the neurone theory, and this conception is not at all interfered with by the newly-won pictures of fibrils. We have, however, made a great step in advance in the direction that we now know how inside a single cell fibers out of other cell domains unite with others which form networks in the cell itself, etc.; how the cell often is only a transfer station for fibers of different origin. A separation in the old sense that each cell exists anatomically for itself alone, entering only externally in relation to neighboring cells, can probably be no longer held without modification. But we must all the more hold fast to the fact that the ganglion cell (including all fibers going into it) forms a biological unit. One can easily conceive that in such units the collection and new distribution of paths of the most different origin may take place without on that account giving up the idea of the unit itself. The establishment of the neurone concept was an important fact. It has made many pictures hitherto confusing easily explicable. It has been unusually heuristic in its effects and has permitted us to understand for the first time certain parts of the nervous system, such as the retina, the bulbus olfactorius, the spinal ganglia and the peripheral sense cells. If it is to be given up to-day it must above all be shown that what is known is irreconcilable with it. This has not been shown."

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[13] Meyer, A.: "Critical Review of the Data and General Methods of Modern Neurology." J. Comp. Neurol., Granville, Vol. VIII (1899), Nos. III and IV.

[14] v. Lenhossek, M.: Review of Bethe's work in Neurol. Centralbl. Leipzig, Bd. (1899), Nos. 6 & 7.

[15] Hoche, A.: "Die Neuronlehre and ihre Gegner." Berlin, 1899, S. 1-52.

[16] Nissl, F.: "Nervenzellen und graue Substanz." Münch, med. Wchnschr., Bd. XLV, 1898, S. 988; 1023; 1060.

[17] Edinger, L., and A. Wallenberg: "Bericht ueber die Leistungen auf dem Gebiet der Anatomie des Centralnervensystems während der Jahre, 1897 und 1898." Schmidt's Jahrbücher, Leipzig, Jahrg. 1899. Bd. CCLXII, S. 65.

In conclusion I may be permitted again to emphasize my own view. The formulation of the neurone doctrine was the equivalent of applying the doctrine of cell-units to the nervous system. The actual application to the nervous system at so late a date of a doctrine long known and generally appreciated for the other tissues of the body is explicable by the fact that it has been only recently that it has been possible to replace the mistaken conception of the extent of a nerve-cell formerly held by the true conception. If the term "nerve-cell" called up in mind the idea which we now hold of the biological unit in the nervous system there would be no necessity for the use of the word "neurone." But until the text-books have been expurgated and the nomenclature employed by teachers and writers becomes more precise, some word other than "nerve-cell" would seem necessary. Any one who has the idea of "contact-relation" inseparably connected in mind with the term "neurone" would do well to give up the use of the word and to use "nerve-unit" or "complete nerve-cell" in its place. But for those who have never considered the theory of contact relation as a necessary part of the neurone doctrine, but have regarded the neurone as the unit in the nervous system corresponding to the cells in other parts of the body, the term can be indefinitely retained and even employed with reverence on account of its historical significance.

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99 "NEUE BEOBACHTUNGEN ÜBER DIE VERÄNDERUNGEN DER PYRAMIDENRIESENZELLEN IM VERLAUF DER PARAPLEGIEEN" (New Observations on the Changes of the Pyramidal Giant Cells Occurring in Paraplegia). G. Marinescu (Deutsche med. Wochenschrift, May 31, 1900, p. 351).

Marinescu has examined the Rolandic area in six cases of compression of the spinal cord with descending degeneration of the pyramidal tract. The duration of the lesions varied from five months to two years. He found alteration of the cells of Betz in all six cases. Where the spinal lesion had been of short duration the cell-body was swollen, rounded, and presented chromatolysis, chiefly central, and some displacement of the nucleus. In cases of longer duration the lesions were more pronounced, and cellular atrophy was observed. The alteration of Betz's cells occurred from a lesion of the pyramidal tract at any level, but it was greater the nearer the lesion was to the cell-body.

In the study of the motor cortex in a case of amyotrophic lateral sclerosis, Marinescu found great alteration of the giant cells. Most of these cells had disappeared, and the few remaining ones were very atrophic and showed chromatolysis and displacement of the nucleus. Marinescu leaves it undecided whether these cellular changes were primary or secondary. SPILLER.